3 NDAC ISSUES
RAISED

3 NDAC ISSUES RAISED DURING DISCUSSIONS OF OTC NSAID WARNINGS

During the September 20, 2002 NDAC meeting, there were Committee discussions about the need for adding a separate warning statement for stomach bleeding and one for concomitant use of multiple NSAID products. These two proposed warnings were not included in FDA's Proposed Rule of August 21, 2002. The Committee also raised the issue of a continuing need for an alcohol warning if a stomach bleeding warning was adopted. In the proposed rule of August 21, 2002, FDA included an alcohol warning in the labeling of OTC ibuprofen as required by final rule published October 23, 1998 [63 FR 56789] and included in 21 CFR 201.322.

3.1 Stomach Bleeding Warning

Considering evidence presented at the NDAC meeting on September 20, 2002, some Committee members suggested adding a separate general "stomach bleeding" warning on OTC NSAID products.

McNeil's review of scientific literature indicates that at recommended OTC doses, ibuprofen appears to have a lower risk of gastrointestinal adverse effects compared with aspirin and other NSAIDs [1,2,3,4,5]. In recent meta-analyses evaluating the occurrence of gastrointestinal complications [1,2], ibuprofen was reported to be the safest of all NSAIDs studied. The crude risk ratios (RR) of the other NSAIDs (including aspirin) that were evaluated ranged up to approximately four-fold higher than ibuprofen. Henry and colleagues [1] noted that adverse gastrointestinal effects for several of the NSAIDs were dose-related. Low dose ibuprofen ($\leq$ 1200 mg) was associated with a pooled RR of 1.6 (95% CI: 0.8 - 3.2) compared with a pooled RR of 4.2 (95% CI: 1.8 - 9.8) for higher dose ibuprofen ($\geq$ 2400 mg). In another study, Gutthann et al [3] estimated the risk of complicated ulcer for NSAID users and non-users and found that compared to users of other NSAIDs, ibuprofen users had the lowest risk of peptic ulcer (odds ratio, 2.1; 95% CI: 1.1 - 4.0). Mellemkjaer, et al [5] reported that of the most commonly used NSAIDs in Denmark, the lowest risk of upper GI bleeding (UGIB) was associated with use of ibuprofen. Ibuprofen dose of < 1000 mg per day was associated with a 2-fold increased risk of UGIB, with the observed/expected (O/E) ratio rising to 3.6 (95% CI: 2.4, 5.1) for an ibuprofen dose of 1000 - 1999 mg per day.

McNeil believes that the current labeling for OTC ibuprofen products is appropriate for safe consumer use. We also recognize that FDA has been implementing OTC labeling modifications that provide more specific language related to organ systems, disease states, and symptoms. As such, McNeil is committed to adopting the specific format and language of warnings proposed by FDA provided that the warnings have a sound scientific basis.

McNeil can support adoption of a general stomach bleeding label warning on OTC ibuprofen and all other OTC Analgesic NSAIDs because GI toxicity including stomach bleeding is noted to occur at recommended doses. It has been suggested that a stomach bleeding warning may be duplicative of language included in the OTC Analgesic NSAID alcohol warning. However, stomach bleeding can occur with use of OTC NSAIDs independent of alcohol use by history. McNeil can support both warnings because each different label warning helps address a public health issue for two different at risk populations.

3.2 Warning for Concomitant Use of Multiple NSAIDs

A report on recent medication use data as provided in Section 3, Consumer Medication Use of McNeil's background package [6] for the September 20, 2002 NDAC meeting suggests that, despite this warning, consumers may concurrently take more than one OTC NSAID. Some possible reasons for this consumer behavior may be that consumers may not know the ingredients of OTC pain relievers, may not know that different pain relievers contain similar ingredients, or may have severe pain states causing the consumer to take additional pain relievers to relieve residual pain. These reported consumer practices might be reduced with labeling changes.

McNeil's review of scientific literature indicates that concurrent use of multiple NSAIDs appears to lead to a further increased GI bleeding risk compared to the risk with single NSAID use [2,3,5]. Gutthann et al [3] conducted a nested case-control study of UGIB or perforation in Canada. Among current NSAID users, multiple NSAID use presented the highest adjusted OR, 9.0 (95% CI: 5.9 – 13.6), of complicated peptic ulcer compared to an adjusted OR of 4.1 (95% CI: 3.4 – 4.8) for single NSAID use. Mellemkjaer and colleagues [5] evaluated the risk of hospitalization for UGIB among a cohort of NSAID users in Denmark. For current users, the O/E ratio of UGIB was 3.61 (95% CI 3.3, 4.0) for NSAID only (not combined with other drugs) compared to the O/E ratio of UGIB of 5.52 (95% CI 4.3, 6.9) for use of NSAID plus aspirin.

FDA's Proposed Rule published of August 21, 2002 shows that the current approved labeling for OTC ibuprofen drugs for adults under the NDA process includes: Warning: "talk to a doctor or pharmacist before using an ibuprofen product if you are already taking any other product that contains ibuprofen or any other pain reliever/fever reducer."

So as to improve consumer awareness of NSAID active ingredients, McNeil supports replacing the current approved warning for OTC ibuprofen with a new warning that provides consumers with the individual names of OTC NSAID active ingredients and that warns against their simultaneous use. McNeil proposes that it would be appropriate to use warning language that is similar to that currently used for other OTC analgesics. For ibuprofen, such a warning might read, "Do not use • with any other product containing ibuprofen or other NSAIDS such as aspirin, ketoprofen, or naproxen sodium.

Additionally, so as to ensure appropriate and consistent consumer labeling, McNeil recommends that FDA require similar labeling changes for aspirin-containing products and for all other OTC NSAID products.

3.3 Alcohol Warning For OTC NSAIDs

For the NDAC meeting, no FDA agenda topics or questions were raised to the Committee about the alcohol warning currently required by final regulation on all OTC internal analgesic/antipyretic drug products. However, the topic of the alcohol warning was raised during NDAC discussions of GI bleeding risks with OTC NSAIDs. Some Committee members expressed unfamiliarity with the alcohol warning's scientific support. They also expressed unfamiliarity with previous FDA Advisory Committee meetings that dealt with this topic. Some Committee members questioned the continued need for an alcohol warning, particularly if a separate stomach bleeding warning were adopted.

The following sections provide McNeil's perspective and scientific view on this issue. They highlight conclusions reached by FDA in the Alcohol Warning Final Rule published on October 23, 1998 [63 FR 56789], a summary of scientific evidence submitted January 29, 1998 by McNeil in response to the Agency's proposed rule of November 14, 1997 to establish alcohol warnings for all OTC adult internal analgesic drug products and an update of recently published studies evaluating GI risks with use of alcohol and OTC NSAID ingredients. McNeil also offers responses to comments submitted to Docket No. 77N-0941 subsequent to the September 20, 2002 NDAC meeting.

3.3.1 FDA'S Alcohol Warning Rulemaking [62 FR 61041] and [63 FR 56789]

3.3.1.1 Overview

The scientific evidence and public health issues related to the need for an alcohol warning on all OTC IAAA drug products, including ibuprofen, have previously been more than fully evaluated by FDA and expert members of its Advisory Committees. At the time of the reviews, Advisory Committees indicated that comparable levels of scientific evidence should be used in applying the need for an alcohol warning on each OTC analgesic ingredient. Therefore, any effort to re-consider the alcohol warning should occur under a formal rule making process with advance notice and full open public discussion, including a comprehensive review of all data for all OTC IAAA ingredients.

In the Alcohol Warning Proposed and Final Rules, the available scientific evidence that was considered included randomized controlled clinical trials, case-control studies, cohort studies, meta-analyses, surveys, case series and case reports. There is considerable variability in the quality of scientific evidence evaluated. It is generally accepted that data are progressively more convincing and less subject to bias and confounding for analytic studies (e.g. randomized controlled trials, cohort studies and case-control studies) than for descriptive data (e.g. surveys, case series and case reports). Associations shown by analytic studies are more likely to be causal associations than associations suggested by descriptive data. Confidence in the results obtained becomes progressively reduced for descriptive data compared to results from analytic studies.

In the Alcohol Warning rulemaking process, scientific evidence presented in favor of a warning on acetaminophen-containing products was based almost exclusively on descriptive data from case reports and case series. The analytic data, from a prospective randomized controlled trial referenced in the Final Rule [7] and a second larger prospective well-controlled study [8], have shown that chronic alcoholics can take maximum daily doses of acetaminophen for two consecutive days without risk of liver injury. In contrast, for aspirin, ibuprofen and other OTC NSAIDs, scientific evidence (presented in rulemaking) that supports an alcohol warning is, for the most part, from analytic studies such as controlled trials, cohort and case-control studies. Case series and case report data of GI bleeding with NSAID and alcohol use was also presented.

3.3.1.2 Regulatory History

At a June 29, 1993 meeting of the NDAC, FDA asked the committee to discuss the need for an alcohol warning for OTC drug products containing acetaminophen. On September 8, 1993, the NDAC and the Arthritis Drugs Advisory Committee met jointly to consider data on the risk of the use of aspirin and other OTC NSAID analgesics by heavy alcohol users or abusers. FDA reviewed scientific evidence, Advisory Committee comments and public comments in both an Alcohol Warning Proposed Rule published on November 14, 1997 [62 FR 61041] and Final Rule published on October 23, 1998 [63 FR 56789].

FDA's Final Rule requires an Alcohol Warning for all OTC drug products, labeled for adult use, containing internal analgesic/antipyretic active ingredients, including ibuprofen. For OTC products containing ibuprofen, the warning states, "If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding."

3.3.1.3 FDA Conclusions

The available scientific evidence considered in FDA's Final Rule included randomized controlled clinical trials, cohort studies, case-control studies, meta-analyses, surveys, case series and case reports. The following comment regarding evaluation of study data is made in the Final Rule:

> "When reviewing these data from various studies, the agency has taken into account the limitations of each study method. Despite the limitations of individual studies, the data generated by each of these methods collectively provided a sound body of evidence from which it is scientifically reasonable to assess risk. Therefore, the agency believes that the collected body of scientific evidence supports the labeled warning."

After having evaluated the clinically relevant data and science, FDA also comments:

> "Given the data available at this time, the agency cannot precisely quantify the increased risk of combining routine heavy alcohol use and these OTC drug products. In order to require an alcohol warning, however, it is not necessary that the agency be able to demonstrate precisely how much the risk is increased. The available data demonstrate clearly that the risk to consumers of combining heavy routine alcohol use with these drug products is greater than the risk of using either alcohol or these drug products alone. These data are sufficient to establish the need for an alcohol

warning on these OTC products. In light of the clearly demonstrated increased risk to consumers, the agency is requiring an alcohol warning about the risk of stomach bleeding on aspirin and other NSAID-containing OTC drug products."

In summary, the Final Rule continues:

"OTC analgesic/antipyretic drug products, including aspirin, are known to cause adverse GI effects, including bleeding. Chronic, heavy alcohol use is also associated with adverse GI effects, including bleeding. Based on the agency's review of a large body of scientific information and in concurrence with expert advisors, FDA had determined that routine, heavy (three or more alcoholic drinks every day) alcohol use in combination with use of OTC analgesic/antipyretic drug products containing NSAID ingredients increases the risk of adverse GI events, including stomach bleeding. The agency believes that the most appropriate public health response to this information concerning risk is to warn consumers who drink three or more alcoholic drinks every day to consult their doctor about their use of these OTC drug products. This conclusion is scientifically based, clinically relevant, and important for the safe and effective use by consumers of OTC analgesic/antipyretic drug products containing NSAID ingredients."

3.3.2 McNeil Submission to FDA'S Alcohol Warning Proposed Rule [62 FR 61041]

On January 28, 1998, McNeil submitted extensive comments to Docket 77N-094W in response to FDA's Proposed Rule of November 14, 1997. Among scientific evidence detailed in McNeil's submission were some epidemiolgic studies of GI risk associated with OTC NSAIDs and alcohol, including a published historical (nonconcurrent) cohort study by Carson [9] and published case-control studies conducted by Henry [10], Peura [11] and Lanas [12]. In addition, McNeil provided to FDA an unpublished report of an epidemiologic study and an unpublished report of an independent re-analysis of a previous epidemiologic study, both of which have been recently published [13,14]; these two publications are reviewed below in Section 3.3.3 of McNeil's summary of recent publications.

Carson et al. [9] conducted a historical cohort study of prescription users of NSAIDs in the United States (i.e., Michigan and Minnesota) using diagnoses from a Medicaid billing database. Patients known to have been dispensed aspirin were excluded. The largest numbers of patients were exposed to ibuprofen, sulindac or indomethacin, respectively. Carson reported that NSAID users who abused alcohol had significantly higher rates of upper GI bleeding UGIB ($p<0.001$) than NSAID users who did not abuse alcohol. Carson

reported that an interaction between NSAIDs and alcohol-related diagnosis (p=0.017) was found, with and without adjustment for the effect of age, sex, and state by logistic regression.

Henry et al. [10] conducted a case-control study in Australia of 644 patients admitted to a hospital with upper GI bleeding (UGIB) or ulcer perforation compared to 1268 community and hospital controls without UGIB. Associations were investigated between UGIB and use of aspirin, non-aspirin NSAID (NANSAID) and alcohol (5 or more drinks per drinking session). Prescribed and nonprescribed NANSAID included diclofenac, diflunisal, ibuprofen, indomethacin, naproxen and sulindac. The odds ratio (OR) for alcohol use in non-users of either aspirin or NASAID was 2.8 (95% CI: 1.9 - 4.0). Among non-aspirin NSAID users, the OR was 3.8 (95% CI: 2.8 - 5.2) for NSAID use without alcohol and 6.0 (95% CI: 3.3 - 11.0) for both NSAID and alcohol use. Among aspirin users the OR was 3.0 (95% CI: 2.2 - 4.0) for aspirin use without alcohol and 8.1 (95% CI: 4.1 - 16.1) for both aspirin and alcohol use. Henry's conclusions state that the concomitant consumption of aspirin with alcohol can significantly affect the risk of major upper GI complications for users of NSAIDs.

Peura et al [11] reported results from a survey of American College of Gastroenterology (ACG) physicians who collected standardized information on 635 cases of GI bleeding and 600 procedure-matched controls who were nonbleeding. When compared to controls, the GI bleeding cases were found to more likely use alcohol (28.6% vs. 16.5% in controls) and more likely to have recently used OTC NSAIDs, such as aspirin, ibuprofen, or naproxen (47.6% vs. 19.4% in controls). The OR (95% CI) for GI bleeding for alcohol use alone was 2.07 (1.48 - 2.88). The OR for GI bleeding was 2.76 (95% CI: 2.03 - 3.74) for patients who currently used OTC NSAIDs and 4.47 (95% CI: 2.73 - 7.32) for patients who combined alcohol use with OTC NSAIDs.

Lanas et al [12] reported associations between use of aspirin and NSAID (including diclofenac, ketorolac, piroxicam) and the development of upper and lower GI perforation from a case-control study of 76 consecutive patients with a diagnosis of GI perforation and 152 matched controls. The calculated OR for GI perforation in patients who had used an NSAID within a week prior to hospitalization was 6.64 (95% CI: 3.6 - 12.2) as compared to those who had not. Other independent risk factors for perforation included alcohol ingestion (OR 3.25; 95% CI: 1.81 - 5.82) and smoking (OR 3.88; 95% CI: 2.15 - 7.0). The combination of NSAID use, smoking, and alcohol use increased the OR for GI perforation to 10.69 (95% CI: 3.82 - 29.87).

McNeil's submission to FDA in 1998 also included case series data from an unpublished multicenter study of adults admitted to a hospital or emergency room for upper GI bleeding. Of 483 cases of upper GI bleeding within the 24-week period of study, 263 patients (54%) had ingested aspirin, ibuprofen, or another NSAID. Of these 263 patients, 108 (41%) ingested alcohol plus an NSAID. Fifty-seven (22%) of the 263 patients had ingested ibuprofen with or without alcohol, and 41 (72%) of the ibuprofen cases occurred with OTC doses.

Collectively, the scientific evidence submitted to FDA by McNeil in 1998 supports an increased risk of GI bleeding associated with use of aspirin, ibuprofen or other OTC NSAIDs and alcohol. McNeil believes recent scientific evidence is sound and consistent with previous data.

3.3.3 McNeil Summary of Recently Published Studies of Alcohol and OTC NSAIDs

Since issuance of the Alcohol Warning Final Rule on October 23, 1998, a number of epidemiologic studies have been published evaluating the GI risk associated with use of aspirin, ibuprofen, and other NSAIDs with alcohol [13,14,15,16,17,18]. Data from these recent publications are consistent with previous scientific evidence and continue to demonstrate an increase in risk of GI complications with the use of alcohol and OTC NSAIDs, including ibuprofen.

Kaufman [13] conducted a case-control study in the United States and Sweden of 1224 patients hospitalized with acute upper GI bleeding compared to 2945 neighbor controls. Kaufman estimated the relative risk for analgesic use at different levels of alcohol use. They found no significant heterogeneity among the relative risk estimates for either aspirin or ibuprofen at different levels of alcohol consumption; that is, both regular aspirin use and regular (at least every other day) ibuprofen use further increased the risk of UGIB in alcohol users. Among regular users of >325 mg of aspirin, the relative risk of acute upper GI bleed for current drinkers was 7.0 (95% CI: 5.2 - 9.3) compared with 5.1 (95% CI: 2.8 - 9.0) for nondrinkers. While Kaufman's data were less stable for regular users of ibuprofen, the relative risk of acute upper GI bleed among current drinkers was 2.7 (95% CI: 1.6 - 4.4) compared with 2.2 (95% CI: 0.8 - 6.0) for nondrinkers. McNeil previously provided an unpublished report of this study to FDA and Advisory Committees during the alcohol warning rulemaking process.

Blot [14] performed an independent re-analysis of data from a case-control study in the United States conducted by the American College of Gastroenterology (ACG) [11]. These further analyses described risks of GI bleeding in relation to recent use (within the past week) of OTC analgesics, tobacco, and alcohol (consumption at any level). After deletion of duplicate records, a total of 627 cases of GI bleeding and 590 procedure-matched controls were available. Blot reported that drinking alcoholic beverages was associated with a two-fold increase in risk of GI bleeding (95% CI: 1.4 - 2.7). Recent users of both aspirin and ibuprofen were associated with an increased risk of GI bleeding; use of OTC ibuprofen resulted in an adjusted OR of 2.4 (95% CI: 1.5 - 3.9) and use of OTC aspirin resulted in an adjusted OR of 2.7 (95% CI: 1.9 - 3.8). In addition, Blot reported that both aspirin and ibuprofen use were linked to increased risks of GI bleeding in both drinkers and nondrinkers. These ACG data from an ACG Bleeding Registry Study [11] were part of the scientific evidence evaluated by FDA in the Alcohol Warning Final Rule [63 FR 56789].

Aalykke [15] performed a case-control study in Denmark of 132 current NSAID (including aspirin) users hospitalized due to bleeding peptic ulcers compared to 136 NSAID user controls without GI complications recruited from the hospital outpatient clinic. Among NSAID users with bleeding peptic ulcer, 42% used aspirin, 33% used other NSAIDs (unspecified), and 25% used both aspirin and NSAIDs. Aalykke found an increased risk (adjusted OR 2.39, 95% CI: 1.16 - 4.89) for bleeding peptic ulcer among NSAID users consuming alcohol (more than five drinks per week).

Neutel and Appel [16] performed a case-control study in Canada of 1083 patients hospitalized for definite severe GI events compared to 14,754 randomly selected non-hospitalized controls using data from hospital discharge and prescription drug plan computerized databases. A history of alcohol abuse by itself led to an adjusted OR of 2.6 (95% CI: 1.9 - 3.7). Neutel found that the presence of ibuprofen and/or naproxen treatment without alcohol abuse was associated with an adjusted OR of 1.9 (95% CI: 1.6 - 2.3) for severe GI events. The combination of ibuprofen and/or naproxen treatment with alcohol abuse resulted in an adjusted OR of 6.5 (95% CI: 2.8 - 15.0).

Lanas [17] conducted a case-control study in Spain of 98 patients admitted to two general hospitals presenting with signs of upper GI bleeding and who were taking low-dose aspirin compared to 147 controls without signs of bleeding that were current users of low dose aspirin. Both cases and control were currently taking daily low dose aspirin (< or = 325 mg) for at least 15 days before study entry. The study's results showed that a history of alcohol use (any consumption) was significantly (p=.0001) more frequent in cases (24.5%)

compared to controls (8.8%). Lanas identified an increased risk (adjusted OR 4.26, 95% CI: 1.71 - 10.40) for bleeding peptic ulcers among low-dose aspirin users with a history of alcohol use.

Adamopoulos [18] conducted a cross-sectional study in Greece of a total of 330 consecutive patients admitted to an emergency department who presented with clinical manifestations of upper GI bleeding and who underwent endoscopy within 12 hours of admission. Of these, a total of 178 patients reported using an NSAID (NSAID user) in the last week; 82 (46%) of which reported use of an OTC NSAID. Endoscopic findings of GI bleeding were found in 98% (174 of 178) of NSAID users. Aspirin use was most commonly reported; less frequently reported was use of ketoprofen, naproxen and other NSAIDs. The group of NSAID users included a significantly greater proportion of alcohol abusers (p=0.01), who were found to bleed mostly from erosive gastritis. Because erosive gastritis instead of bleeding ulcer was the most frequent endoscopic finding in the alcohol abuse subgroup, the authors concluded that alcohol abuse does increase the risk of upper GI bleeding in NSAID users.

3.3.4 Wyeth Comments to Docket No. 77N-0941 About Alcohol Warning

Wyeth Consumer Healthcare (Wyeth) submitted comments on November 19, 2002 to FDA Docket No. 77N-0941, which included a recommendation that the alcohol warning on OTC ibuprofen be removed. McNeil's comments regarding this recommendation follow:

3.3.4.1 Well-Established GI Bleeding Risks

Wyeth states that it is well established that alcohol and NSAID use are independent risk factors for GI bleeding. Wyeth's statement is in agreement with the scientific data and evidence reviewed in the Alcohol Warning Final Rule, which served, in part, to support requiring an alcohol warning on OTC NSAID products. Despite these well-established risk associations, Wyeth cites a lack of evidence that alcohol "potentiates" the risk of GI bleeding from using OTC analgesics and, based on this lack of potentiation, believes that the alcohol warning should be removed from OTC ibuprofen.

Wyeth's argument confuses interpretation of well-established risk information. If an individual uses either alcohol or an NSAID, that individual is at an increased risk for GI bleeding since both are independent risk factors for GI bleeding. If the same individual uses both alcohol and an NSAID, that individual is now at a further increase in risk than if that individual had taken either one alone. The adverse health effect from GI bleeding is

greater from exposure to two known risk factors than from exposure to one alone. Hence, from a harm reduction point of view, consumers should be warned that taking both factors puts them at a higher risk of GI bleeding than taking only one of them.

3.3.4.2 McNeil's Assessment of Wyeth's Published Literature Update

Wyeth provides an update of published literature from an endoscopy study reported by Lanza [19], a pharmacokinetic study by Melander [20], a cross-sectional study by Pulanic [21], and epidemiologic studies by Carson [9], Kaufman [13], and Neutel and Appel [16]. Wyeth concludes that data from clinical trials as well as epidemiological studies show that alcohol does not adversely affect the GI safety of ibuprofen.

McNeil's assessment of the studies identified by Wyeth follows. Overall, McNeil believes there is evidence from these studies that are consistent with a higher GI risk associated with use of alcohol and OTC NSAIDs, including ibuprofen. Wyeth's published literature update does nothing to change the GI risk assessments regarding use of alcohol and OTC NSAIDs, including ibuprofen.

The endoscopy study reported by Lanza et al. [19] examined the effects on gastroduodenal mucosa of acute exposures to alcohol and either aspirin, ibuprofen or placebo tablets in normal volunteers. The medications (with or without alcohol) were taken four times in one day (before each meal and at bedtime). The next morning, the study subjects were examined endoscopically. The number of subjects with evidence of gastric mucosal damage (endoscopic scores of 1, 2, 3, or 4) were 1 of 10 for placebo, 2 of 10 for alcohol only, 1 of 10 for ibuprofen only, 5 of 10 for alcohol and ibuprofen, 10 of 10 for aspirin only, and 9 of 10 for aspirin and alcohol. The sample sizes were small and no significant differences between alcohol, ibuprofen and placebo groups were found. The addition of alcohol to either ibuprofen or aspirin resulted in more subjects having higher gastric endoscopic scores compared to those subjects who received only ibuprofen or aspirin. Lanza reported that the addition of alcohol to ibuprofen approached statistical significance ($0.1>p>0.05$) for a worsening of gastric damage. Among the study's conclusions, the authors stated that, "The addition of alcohol to all drugs increased the damage seen in the stomach, although the only difference approaching significance was seen with the ibuprofen-alcohol combination over ibuprofen alone". The study is limited by the acute nature of the exposure and the small sample size, but it provides evidence that the effect of ibuprofen and alcohol together is greater than the effect of either agent alone on the gastric mucosa.

The pharmacokinetic study of Melander et al. [20] examined the effect of a single dose of either aspirin or ibuprofen or acetaminophen on the blood levels of ethanol (ingested one hour after analgesic administration) in healthy volunteers. The investigators reported that none of the analgesics had an effect on the ethanol peak concentrations, time to peak concentration and area under concentration curves. GI safety was not assessed and its relevance to the current issue is uncertain at best.

The study by Pulanic et al. [21], while represented by Wyeth as a prospective clinical trial, is in fact a cross-sectional study of 367 patients treated at a single hospital in Croatia for bleeding gastroduodenal lesions over a 15-month period. The patients were administered a questionnaire to ascertain information about drug use in the two months preceding the bleeding event as well as lifestyle information (e.g., smoking habits and alcohol consumption). The publication simply reports the lifestyle information of only the 88 patients who reported use of an ulcerogenic drug preceding the bleeding event. No data on risk factors are presented for the 279 patients with GI bleeding who did not use ulcerogenic drugs. Only 4 of 88 (4.5%) patients reporting use of ulcerogenic drugs, also reported using alcohol (defined as greater than 40 g/day for women and 60 g/day for men). Only nine of the 88 patients reported using ibuprofen and it was not reported whether any of these nine also used alcohol. The authors indicate that none of the risk co-factors (including alcohol use) were strongly associated with the use of NSAIDs and upper GI bleeding. Wyeth's conclusions must be examined in light of the study's scientific frailty including the study design limitations and inadequate power to examine the joint GI effects associated with use of ibuprofen and alcohol,

The case-control study by Kaufman et al. [13] concluded, "The findings suggest acute UGIB is similarly associated with the use of the two most common nonprescription NSAIDs, aspirin and ibuprofen, at all levels of alcohol consumption." Wyeth notes, "...that there was no consistent trend between relative risk and increasing alcohol use..." for regular (at least every other day) use of ibuprofen, but the same pattern was observed for aspirin. Risk estimates would be expected to be more consistent for aspirin than for ibuprofen because of the much larger sample size for aspirin compared to ibuprofen. There were 809 regular users and 632 occasional users of aspirin in the study, compared to only 118 regular users and 227 occasional users of ibuprofen. Wyeth claims that the increased risk of bleeding reported for ibuprofen in current drinkers was "primarily driven by the spurious finding that regular ibuprofen users whose alcohol intake was <1 drink per week had a high relative risk of 4.4 (1.8 - 11)". However, based on data for regular ibuprofen users in Table 3 on page

3193 of Kaufman et al, the calculated crude relative risk estimate for current alcohol consumption of 14 or more drinks per week is 3.4 (exact 95% CI: 1.2 - 10.9). As the estimates and CI in Table 3 show, the data are consistent with a 2-fold increase in the risk of upper GI bleeding for regular ibuprofen use in never-drinkers, ex-drinkers, and current drinkers at all levels of consumption. The risk of UGIB increases with increasing levels of alcohol consumption, which justifies the author's conclusion that "the incidence of UGIB is highest among persons who are both heavy drinkers and users of aspirin or ibuprofen."

Both the studies of Carson et al. [9] and of Neutel and Appel [16] used computerized medical databases (the Medicaid billing databases in Michigan and Minnesota for Carson et al. and the Saskatchewan Health Databases for Neutel) to identify records of individuals who received prescriptions for NSAIDs and to ascertain diagnoses of GI bleeding events. Neither study had information on alcohol consumption, but both identified individual records with diagnoses (using information in the medical databases) of chronic alcoholism as a surrogate for alcohol use. Carson et al. used diagnoses of alcohol-related diseases (including alcoholic psychosis, delirium tremens, alcohol intoxication, alcoholic cirrhosis, and alcoholic cardiomyopathy) to identify chronic alcoholics. Neutel used records of alcoholism-related treatments or prescriptions for a drug used to treat alcoholism (i.e., disulfiram). Only NSAID users were included in the Carson study, and thus only the GI effect of alcohol abuse in NSAID users could be estimated, whereas, the Neutel study could estimate the separate and joint GI effects associated with alcohol and NSAID use. Wyeth criticizes the Neutel study because chronic alcoholism was used as a surrogate for alcohol consumption and daily alcohol exposure was not measured, but the same criticism applies to the Carson study.

The results from both studies [9,16] are consistent with a higher risk of GI bleeding/events in NSAID users with alcohol abuse compared to those who used NSAIDs without alcohol abuse. Carson reported that NSAID users who abused alcohol had significantly higher rates of upper GI bleeding UGIB ($p<0.001$) than NSAID users who did not abuse alcohol. No relative risk estimates for alcohol abuse were provided in the publication for all NSAID users or individual NSAID users. The study reported that an interaction between NSAIDs and alcohol-related diagnosis ($p=0.017$) was found, with and without adjustment for the effect of age, sex, and state by logistic regression. Although this publication provided no relative risk estimates for alcohol abuse among all NSAID users, the Wyeth letter reports that the OR was 1.34 (95% CI: 0.4 - 4.3) for UGIB among ibuprofen users with an alcohol-related diagnosis compared to the entire population of ibuprofen users.

Neutel found that a history of alcohol abuse by itself led to an adjusted OR of 2.6 (95% CI: 1.9 - 3.7). The presence of ibuprofen and/or naproxen treatment without alcohol abuse was associated with an increased risk of severe GI events (adjusted OR 1.9, 95% CI: 1.6 - 2.3). The combination of ibuprofen and/or naproxen treatment with alcohol abuse resulted in an adjusted OR of 6.5 (95% CI: 2.8 - 15.0).

3.3.4.3 McNeil's Evaluation of Wyeth's Critiques

Wyeth commissioned two critiques of a recent publication by Blot and McLaughlin [14], which provided an independent re-analysis of data from the ACG Bleeding Registry study [11]. Physician consultants, James D. Lewis, MD, MSCE and Jeffrey L. Carson, MD, each provided a critique for Wyeth.

In its comments to the docket, Wyeth notes that the Blot and McLaughlin study had significant methodological shortcomings, including (1) the non-randomized, non-blinded manner of the study; (2) an "...obvious selection bias"; (3) inappropriate controls and cases that "...almost were certain to have less exposure to NSAIDs..."; and (4) lack of critical information on duration of NSAID use. Based on these, Wyeth believes "...it is difficult and inappropriate to draw any conclusions from this study."

The review by Dr. Lewis indicated that there were several "potential flaws", including the possibility of selection bias. He stated that the controls, selected from patients undergoing endoscopy by the same physicians who identified the cases, might have lower NSAID use because of the GI problems that led them to see the doctor, and cited data from the Slone survey [22] showing a higher prevalence of NSAID use in the general population than reported for the subjects in the ACG study [11]. He also speculated that there may be some selection bias for the cases, in particular, that the most seriously ill GI bleeding patients were over represented in the case group. Dr. Lewis also mentioned, "...information bias that could have affected the results of this study.", suggested that the cases may have been more intensely interviewed than the controls, and raised the possibility of misclassification and confounding.

Dr. Carson stated, "...there are many weaknesses of this study...", including combining upper and lower GI cases, and selection of controls. Dr. Carson stated that the controls should have been selected from the same community as the cases. He also indicated that the statistical analysis should not have controlled for dyspepsia, and claimed that duration

of NSAID exposure is known to be related to GI bleeding but this information was not adequately captured.

A key issue in any case-control study is the selection criteria for cases and controls. Dr. Carson states that the controls should come from the general community. A basic epidemiologic tenet of case-control studies calls for the controls to come from the same "study base" or underlying population as the cases. Since the cases were identified from gastroenterologists' records, and not random samples of all cases of GI bleeding in the community, the most appropriate controls would arise from the same gastroenterologists' practices, exactly as was done in the ACG survey. It is possible that use of NSAIDs would be lower in patients being seen for GI disorders, but this applies to both the cases and controls (i.e., each control had undergone the same procedure as the corresponding case), thus reducing the possibility of bias. Furthermore, a significantly higher percentage of the cases than controls had prior episodes of GI bleeding, thus more cases than controls may have been advised to limit NSAID use. The Slone survey estimated a higher prevalence of NSAID use in the general population, not in patients undergoing endoscopy. With differences in the populations studied and in the methods of ascertaining NSAID use, differences in the prevalence estimates are to be expected. What is critical is that the NSAID ascertainment procedures be the same for the cases and controls, which was the attempt of the ACG survey. While Dr. Lewis expressed concern about case selection, Dr. Carson specifically indicated that a real strength of the study is that the cases are well defined.

Dr. Lewis mentioned the possibility of incomplete adjustment for confounding, while Dr. Carson stated that dyspepsia should not have been adjusted for. Controlling for dyspepsia is appropriate, however, since it tends to remove differences between cases and controls and level the playing field for the evaluation of risks associated with NSAID use. One can never be sure that confounding is completely eliminated, but Blot and McLaughlin attempted to minimize its effects by adjusting for potential confounding factors in the statistical analyses.

Dr. Carson also mentioned that duration of exposure is critical, but this position is not well established. Indeed, it seems that current and recent use and dose are the critical factors in NSAID-associated GI bleeding risk. The ACG study did have data on the most relevant risk period.

The two critiques pointed out some of the same concerns that Blot and McLaughlin expressed in their publication. Indeed, Blot and McLaughlin explicitly state that the ACG study had limitations, and that the results "are not definitive" and should be viewed as "more useful for generating, or refining, the hypotheses". Dr. Lewis' overall conclusion that, "while the data from the ACG survey are interesting, these data alone are insufficient to prove that use of OTC NSAIDs increases the risk of GI bleeding", in fact, is not much different than that of Blot and McLaughlin.

It is noteworthy that the findings from the Blot and McLaughlin analyses are completely consistent with the published pharmacoepidemiologic literature on the effects of NSAID use, as well as alcohol intake, on the risk of GI bleeding. The findings in fact are in line with what would be expected from extrapolation of the observed higher risks of GI bleeding following higher dose NSAID use, with what has been seen in other studies of GI bleeding in relation to OTC or other low dose NSAID usage, and with what has been observed about the role of alcohol consumption on GI bleeds. None of this supporting evidence is mentioned in the consultants' critiques that are included in Wyeth's submission to the docket.

In summary, the Wyeth critiques of the Blot and McLaughlin analyses of the ACG data on GI bleeding offer mainly speculation about potential theoretical weaknesses and add little beyond what have already been previously acknowledged as shortcomings by the authors themselves. While the Blot and McLaughlin results are clearly not definitive, they support the consensus evidence that the risk of GI bleeding is greater when alcohol and NSAIDs are used together than when they are used alone.

3.3.5 Conclusions Regarding Alcohol Warning

McNeil believes that an alcohol warning is appropriate for OTC ibuprofen and all other OTC NSAIDs, as required by Final Rule dated October 23, 1998 and included in the Proposed Rule to amend the TFM dated August 21, 2002. The scientific evidence and public health issues related to the need for an alcohol warning on all OTC IAAA drug products, including ibuprofen, have previously been more than fully evaluated by FDA and expert members of FDA Advisory Committees.

Recently published data are consistent with previous scientific evidence and continue to demonstrate an increase in risk of GI complications with the use of alcohol and OTC

NSAIDs, including ibuprofen. Wyeth's published literature update does nothing to change the GI risk assessments.

It is appropriate to retain the alcohol warning as it exists and to adopt a separate general stomach bleeding label warning for OTC ibuprofen because each of these warnings would be directed to two different at risk populations.

If the alcohol warning was removed from OTC ibuprofen, it might lead consumers to conclude they should select ibuprofen as the only safe analgesic choice if they consume alcohol.

Should FDA wish to re-consider the alcohol warning, this should only occur under a formal rule making process with advance notice and full open public discussion, including a comprehensive review of all scientific data for all OTC IAAA ingredients.